REMARKS/ARGUMENTS

Claims 1, 3-4, 7-8, 10-23, 32-33, and 50-52 are pending in this application and presented for examination. Claims 1, 3-4, 7-8, 10-23, 32 and 50-52 have been amended. No new matter has been entered with the foregoing amendments. Reconsideration in view of the foregoing amendments and following remarks is respectfully requested.

I. FORMALITIES

Claim 1 has been amended to recite a "synthetic" monomeric cyclic B-chain peptide. Support for the term "synthetic" is found, for example, at page 23, under the heading "Solid-phase peptide synthesis," and on page 24, under the heading "characterization" especially the first line wherein it states that the "The purity of the *synthetic* peptide…".

The term "analogue" has been deleted from claim 1, as well as claims 3-4, 7-8, 10-23, 32 and 50-52 and the term "peptide" has been used in lieu thereof. The term "peptide" is recited in claim 1 as filed.

Further, the phrase "modification of a turn or loop moiety," as well as the phrase "the B-chain of the relaxin superfamily protein, the modification involving selection of at least a first and a second amino acid residue with an alpha-helix or beta-strand carbon separation distance of less than six angstroms and cross-linking the first and second amino acids" have been deleted. Claim 1 now recites that the claimed cyclic peptide:

> …has an intrapeptide cyclization modification to produce a cross-link between a first amino acid within a range of amino acid positions 2 and 8 and a second amino acid within a range of positions 21 and 26 of each of said peptide sequences, wherein the cross-link conformationally constrains the peptide, and wherein said intrapeptide cyclization is via the formation of a covalent bond between the side chains of said first and second amino acids or a disulfide bond between two cysteine residues, wherein said two cysteine residues are substituted for said first and said second amino acids, or a thioether bond between a substituted cysteine residue at said first or said second amino acid and a halogenated amino acid residue at the other position, either directly or via a spacer group.

The changes to claim 1 are supported starting at page 13, line 7 of the specification, to the bottom of page 14, as well as claims 4, 8, 10, 11 and 13 as filed.

In addition to the foregoing changes, claim 1 has also been amended to delete the peptides "insulin, "IGF-I and "IGF-II," to further simplify and focus the claimed subject matter. Moreover, the peptides are now recited by SEQ ID NOs to further clarify the claim language. These changes embody preferred peptides of the invention. In claim 14, the term "INSL3" has been replaced by --INSL--. Support is found, for example, in paragraph [0007] of US Patent Publication No. 2007/0004619.

In view of the foregoing support, Applicants believe that no new matter has been entered and respectfully request that the Examiner enter the claim amendments.

Applicants believe that the following response and amendments to the claims place the application in condition for allowance. As the generic claim is allowable, Applicants are entitled to a reasonable number of species. MPEP § 806.04, and 37 CFR § 1.141 provide that *an allowable generic* claim may link *a reasonable number of species* embraced thereby. Therefore, Applicants believe that the withdrawn claims should now be rejoined, and respectfully request that the Examiner do so and examine them on the merits.

II. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner maintained the rejection of claims 1, 3, and 32-33 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner has objected to the use of the term "analogue." In an earnest effort to advance prosecution of the subject application, Applicants have amended claim 1 to more particularly point out and distinctly claim the subject matter of the invention. In this regard, the term analogue has been deleted in claim 1, as well as throughout the claim set and the term "peptide" has been substituted therewith. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

With respect to the terminology of i) "modification of a turn or loop moiety, " ii) "an alpha-helix or beta-strand carbon separation distance of less than six angstroms" and iii) "cross-linking the first and second amino acids," Applicants have amended claim 1 to recite with more specificity, the type of modifications to the claimed peptides. More particularly, claim 1 now recites:

> ...cyclic peptide has an intrapeptide cyclization modification to produce a cross-link between a first amino acid within a range of amino acid positions 2 and 8 and a second amino acid within a range of positions 21 and 26 of each of said peptide sequences, wherein the cross-link conformationally constrains the peptide, and wherein said intrapeptide cyclization is via the formation of a covalent bond between the side chains of said first and second amino acids or a disulfide bond between two cysteine residues, wherein said two cysteine residues are substituted for said first and said second amino acids, or a thioether bond between a substituted cysteine residue at said first or said second amino acid and a halogenated amino acid residue at the other position, either directly or via a spacer group.

As amended, claim 1 sets forth with particularity that the modification to the B-chain are via the formation of i) a covalent bond between the side chains of the first and second amino acids or ii) a disulfide bond between two cysteine residues, wherein the two cysteine residues are substituted for the first and said second amino acids, iii) or a thioether bond between a substituted cysteine residue at the first or the second amino acid and a halogenated amino acid residue at the other position, either directly or via a spacer group. In this regard, the Examiner's attention is respectfully directed to page 13, lines 19-23, which sets forth the claimed features for conformationally constraining the B-chain. As claimed, the first amino acid is within a range of amino acid positions 2 and 8 and a second amino acid is within a range of positions 21 and 26 of each of the peptide sequences.

In view of the amendments to claim 1, as well as the other claims, Applicants respectfully request that the Examiner withdraw the rejection.

III. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1 and 3 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In brief, the Examiner argues that that the claims are broadly described without the requisite number of species. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Applicants have amended the claims to recite the modification of only 7 discrete starting molecules set forth by SEQ ID NOs 1-3 and 7-10, to make monomeric cyclic peptides. The claimed modifications conformationally constrain each of the claimed molecules. The conformational constraint is accomplished via various modification techniques such as the formation of a covalent bond between the side chains of the first and second amino acids or a disulfide bond between two cysteine residues, wherein the two cysteine residues are substituted for the first and said second amino acids, or a thioether bond between a substituted cysteine residue at the first or the second amino acid and a halogenated amino acid residue at the other position, either directly or via a spacer group. The first amino acid is within a range of amino acid positions 2 and 8 and a second amino acid is within a range of positions 21 and 26 of each of the peptide sequences, as claimed.

These monomeric, cyclic peptides bind to a biological target of the relaxin superfamily protein such as IGFR-I, IGFR-II, LGR7 and LGR8. As amended, the method for modification is well defined as claimed. In this regard, the Examiner's attention is respectfully directed to paragraph [0067] as published in the US Patent Publication No. 2007/0004619:

> [0067] (ii) cyclizing via the formation of a covalent bond between the side chains of two residues, such as an amide bond between a lysine residue and either an aspartic acid or glutamic acid residue, or a disulfide bond between two cysteine residues, or a thioether bond between a cysteine residue and a halogenated amino acid residue, either directly or via a spacer group as described in (i) above. The residues contributing the side chains may be derived from the B-chain sequence itself, or may be incorporated into or added on to the B-chain sequence for this purpose; and...

This cross-linking of the first and second amino acids will conformationally constrain the peptide.

Further, the specification clearly teaches how the claimed cyclic peptides in accordance with claim 1 are produced (for example at page 13, line 12, bridging to page 14, line 5). Further, Examples 1 and 2 (pages 23 to 26) demonstrate the production of cyclic peptide analogues of the B-chain of two members of the relaxin superfamily, relaxin 1 and INSL3 in which the peptide is produced by modification as claimed.

Examples 1 and 2 (pages 23 to 26) demonstrate the production of cyclic peptide analogues of the B-chain of two members of the relaxin superfamily, relaxin 1 and INSL3 in which the peptide is produced by modification. The sequences of these analogues are shown in Figure 3 of the present specification, along with an additional member. Specific binding of the peptides is demonstrated in Figures 1 (receptor LGR8) and 2 (receptor LGR7), while antagonistic activity of the cINSL3a analogue against INSL3 at LGR8 is shown in Figure 4.

In view of the amendments, Applicants assert that the scope of claim 1, insofar as it relates to the recited relaxin superfamily proteins relaxin 1, 2 and 3 and INSL3, 4, 5, 6, is fully commensurate with the disclosure provided in the specification. The seven relaxin superfamily proteins now recited in amended claim 1 can be clearly divided into two related sub-groups, relaxin proteins on the one hand and INSL proteins on the other. Figure 3 clearly provides examples of cyclic peptides produced in accordance with the claims for members of each subgroup, namely relaxin 1 and INSL3. Accordingly, it is respectfully submitted that in view of this exemplification and the clarification provided in the amended claim, Applicants are entitled to protection across the entire breadth of amended claim 1.

In the present case, the written description requirement is clearly satisfied as the claimed genus is now well defined and has a representative number of species by actual reduction to practice, the drawings of the molecular structure are clearly set forth in Figure 3 and the specific physical binding of the analogues is demonstrated in Examples 1 and 2. In Figures 1 and 2, the binding to receptors LGR8 and LGR7 is illustrated, while antagonistic activity of the cINSL3a analogue against INSL3 at LGR8 is shown in Figure 4. Clearly, Applicants have

satisfied the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

IV. REJECTION UNDER 35 USC § 101

Claims 1, 3 and 32-33 were rejected under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Applicants have amended claim 1 to recite that the monomeric, cyclic B-chain peptide of a B-chain of a relaxin superfamily member protein is *synthetic*. As such, the claimed peptide is a non-naturally occurring composition. Accordingly, the recited subject matter is patent eligible. Accordingly, Applicants request that the Examiner withdraw the rejection.

V. REJECTION UNDER 35 USC § 102(b)

The Examiner has maintained the rejection of claims 1 and 3 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,911,997 (Schwabe *et al.*). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Under MPEP § 2131:

> [a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Schwabe *et al.* teach in Figure 1, Relaxin-Like Factor (RLF) being composed of an A-chain and a B-chain, *i.e.*, two subunits joined to form a heterodimer. The "heterodimer" of Schwabe *et al.* is different than the "monomer" of the claimed invention. A dimer is defined as "[a] molecule which consists of two similar (but not necessarily identical) subunits. The term could also be used as a verb referring to the act of the two subunits coming together (to dimerize)." A heterodimer is defined as follows: "[a] dimer in which the two subunits are

different." As the Examiner is well aware, any dictionary definition of "dimer" or "heterodimer" would be the same[1].

In addition, the enclosed reference article by Ivell (Reviews of Reproduction, 1997, 2: 133-138) relating to relaxin-like factor (RLF), is the subject of the RLF of Schwabe *et al.* In this regard, the Examiner's attention is respectfully directed to page 135 of this document (top of the left hand column), wherein it is stated:

"*the human molecule, chemically synthesized like relaxin as an A-B heterodimer (Bullesbach and Schwabe, 1995)* ..." [Emphasis added].

As such, an RLF molecule comprising A and B chains, whether cyclized or not, is, by definition, a heterodimer. A person skilled in the art would clearly recognize that the peptide of Schwabe *et al.* is a dimer (comprising both A and B chains). In fact, Schwabe *et al.* teaches at column 2, lines 11-15:

> Among the structural features shared between relaxin and the remaining members of the insulin-related family of hormones are molecular weight, *a "two-chain" structure comprising a B-chain, a connecting C-peptide, and an A-chain, and the number and disposition of disulfide links.*

Moreover, the Examiner recognizes, on page 14 of the Office Action, that the cited peptide of Schwabe shows "the B-chain of RLF [is] linked with the A-chain of RLF." With respect to the Examiner's statement on page 18 of the Office Action that "it is noted that Figure 1 [of Schwabe] depicts one specific structure therefore the peptide is monomeric," is clearly without any basis according to the well-recognized definitions of "dimer" and "heterodimer" used in the art.

In stark contrast, the claimed peptide is a monomer, *i.e.*, a monomeric, cyclic B-chain peptide. The monomer as claimed is a cyclic B-chain peptide. Unlike the heterodimer of Schwabe *et al.*, the claimed invention is a monomer, *i.e.*, a single B chain subunit. Schwabe teaches two chains both an A-chain and a B-chain (the Examiner's attention is respectfully directed to the legend for FIG. 2 in column 3, lines 49-60), whereas the claimed monomeric

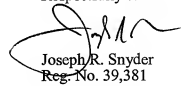
[1] See the enclosed Pharmaceutical Biomolecules glossary & taxonomy web page last visited May 19, 2009.

peptide is drawn to the B-chain only. As a heterodimer is not a monomer as claimed, Schwabe *et al.* do not anticipate the present invention. As such, Applicants request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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Comments? Questions? Revisions? mchitty@healthtech.com

Last revised December 26, 2007

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Genomic biology & chemistry Map: Finding guide to terms in these glossaries Site Map
Related glossaries include: Biology: DNA, Glycosciences, Pharmaceutical biology, Proteins, RNA, Sequences, DNA & beyond

amino acids: Proteins glossary

base, base pair: Sequences, DNA & beyond glossary

biological macromolecules: DNA, RNA and proteins. This term is used particularly in reference to structural **modeling**.

biomolecular interactions: Studies of membranes, **proteins** and peptides, and drug interactions with proteins and **DNA,** from the molecular level to the whole organism using a broad spectrum of biophysical, synthetic and biological methods. [School of Biological and Chemical Sciences, Birbeck, Univ. of London, UK] http://www.bbk.ac.uk/bcs/research/bmi.html

Narrower terms: Proteomics protein- DNA interactions, protein- protein interactions, protein- RNA interactions

Related terms: Omes & omics glossary: interactome, interactomics, kinomics

biomolecules: Wikipedia http://en.wikipedia.org/wiki/Biomolecule

An organic molecule, part of a living organism. Includes **proteins, DNA, RNA.**

List of biomolecules, Wikipedia http://en.wikipedia.org/wiki/List_of_biomolecules

biopolymers: Biomaterials & Bioengineering glossary

carbohydrate binding proteins CBPs: Proteins glossary

carbohydrates: Glycosciences

characterization: Can include determining identity, physical chemistry data, purity, potency, quality, stability, strength, **pharmacokinetics**, dose response, and **efficacy**.

I am still trying to understand all the nuances of "characterize" and "characterization" of **genes, genomes, proteins** and **proteomes** and how these relate to **annotation** and would welcome any insights from people working in these areas.

Related terms: specified biotechnology product, well characterized; characterization, protein Proteins glossary; Bioinformatics glossary annotation

compound: A pure and homogeneous substance consisting of atoms or ions of different elements in definite proportions, usually having properties unlike those of its constituent elements. A compound can be broken down into two or more other substances by chemical means. Glossary, Life Sciences Data Archive, NASA, 2006 http://lsda.jsc.nasa.gov/common/glossary.cfm

compound (chemistry): Wikipedia http://en.wikipedia.org/wiki/Compound_(chemistry)

DNA: DNA glossary

Dalton: Unit of mass equal to the unified atomic mass (atomic mass constant). [IUPAC Compendium] After John Dalton (1766-1844) British chemist and physicist.

Frequently used in biochemistry to express molecular mass, although the name and the symbol [Da] have not been approved by CIPM [Comité international des poids et mesures] or ISO [International Organization for Standardization]. [IUPAC Quantities]

dimer: A molecule which consists of two similar (but not necessarily identical) subunits. The term could also be used as a verb referring to the act of the two subunits coming together (to dimerize). 09 Oct 1997 [OMD]

drug: Drug approvals glossary

glycobiology, glycoproteins, glycoscience, glycotechnology: Glycosciences

heterodimer: *biochemistry* A **dimer** in which the two subunits are different.

isomer: Molecules with identical molecular formulas but different structural formulas[+]. [Fred Senese, General Chemistry Glossary, Frostburg State University, 2001]
http://antoine.frostburg.edu/chem/senese/101/glossary.shtml

kDA: Kilo Dalton

light scattering: About light scattering, Precision Detectors, US
http://www.lightscatter.com/AboutLightScattering.html

macromolecular complexes: It is now clear that most functions in the cell are not carried out by single protein enzymes, colliding randomly within the cellular jungle, but by macromolecular complexes containing multiple subunits with specific functions (Alberts 1998 ⊠). Many of these complexes are described as "molecular machines." Indeed, this designation captures many of the aspects characterizing these biological complexes: modularity, complexity, cyclic function, and, in most cases, the consumption of energy. Examples of such molecular machines are the replisome, the transcriptional machinery, the spliceosome, and the ribosome. Molecular Machines: Putting the Pieces Together, Eva Nogales[a] and Nikolaus Grigorieff[b] Journal of Cell Biology, 152 (1): F1-10, January 8, 2001 http://www.jcb.org/cgi/content/full/152/1/F1

macromolecular systems: Complexes or cellular systems composed of macromolecules (**proteins, DNA, RNA**, polysaccharides, etc.) such as RIBONUCLEOPROTEINS, CHROMATIN, MULTIENZYME COMPLEXES and other **multimeric proteins**. MeSH

macromolecule (polymer molecule): A molecule of high relative molecular mass, the structure of which essentially comprises the multiple repetition of units derived, actually or conceptually, from molecules of low relative molecular mass. Notes: 1. In many cases, especially for synthetic **polymers**, a molecule can be regarded as having a high relative molecular mass if the addition or removal of one or a few of the units has a negligible effect on the molecular properties. This statement fails in the case of certain macromolecules for which the properties may be critically dependent on fine details of the molecular structure. 2. If a part or the whole of the molecule has a high relative molecular mass and essentially comprises the multiple repetition of